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<b>(21) International Application Number:</b> PCT/US98/12711 <b>(22) International Filing Date:</b> 18 June 1998 (18.06.98)  <b>(30) Priority Data:</b> 08/895,184 16 July 1997 (16.07.97) US  <b>(71) Applicant (for all designated States except US):</b> ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> CLARK, Abbot, F. [US/US]; 5603 Rachel Court, Arlington, TX 76017 (US).  <b>(74) Agents:</b> YEAGER, Sally, S. et al.; Alcon Laboratories, Inc., R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		<b>(81) Designated States:</b> AU, BR, CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> THE USE OF ANGIOSTATIC STEROIDS IN PHOTODYNAMIC THERAPY  <b>(57) Abstract</b>  Methods for treating ocular neovascularization using photodynamic therapy in combination with an angiostatic steroid are disclosed.		

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5           **THE USE OF ANGIOSTATIC STEROIDS IN PHOTODYNAMIC THERAPY**

10           **Field of the Invention:**

          This invention relates to the use of angiostatic steroids in photodynamic therapy (PDT).

**Description of the Related Art:**

15           Steroids functioning to inhibit angiogenesis in the presence of heparin or specific heparin fragments are disclosed in Crum, et al., *A New Class of Steroids Inhibits Angiogenesis In The Presence of Heparin or Heparin Fragment*, Science, 230:375-378, December 20, 1985. The authors refer to such steroids as "angiostatic" steroids. Included in the new class of steroids found to be angiostatic are cortisol, cortexolone, and several dihydro and tetrahydro derivatives.

20           In a follow up study directed to testing a hypothesis as to the mechanism by which the steroids inhibit angiogenesis, it was shown that heparin/angiostatic steroid compositions caused dissolution of the basement membrane scaffolding to which anchorage dependent endothelia are attached resulting in capillary involution; see, Ingber, et al. *A Possible Mechanism for Inhibition of Angiogenesis by Angiostatic Steroids: Induction of Capillary Basement Membrane*

25           *Dissolution*, Endocrinology 119:768-775, 1986.

          A group of tetrahydrosteroids useful in inhibiting angiogenesis is disclosed in U.S. Patent No. 4,975,537, issued to Aristoff, et al. The compounds are disclosed for use in treating head trauma, spinal trauma, septic or traumatic shock, stroke, and hemorrhage shock.

30           In addition, the patent discusses the utility of these compounds in embryo implantation and in the treatment of cancer, arthritis, and arteriosclerosis. The compounds are not disclosed for ophthalmic use. Some of the tetrahydrosteroids disclosed in Aristoff, et al. are disclosed in U.S. Patent No. 4,771,042 in combination with heparin or a heparin fragment for inhibiting

angiogenesis in a warm blooded animal. The patent does not disclose the combination for ophthalmic use.

Compositions of hydrocortisone, "tetrahydrocortisol-S," and U-72,745G, each in combination with a beta cyclodextrin have been shown to inhibit corneal neovascularization. Li, et al., *Angiostatic Steroids Potentiated by Sulphated Cyclodextrin Inhibit Corneal Neovascularization*, Investigative Ophthalmology and Visual Science, 32(11):2898-2905, October, 1991. The steroids alone reduce neovascularization somewhat but are not effective alone in providing for regression of neovascularization.

There are currently no effective therapies for the treatment of ocular neovascular diseases which do not include the destruction of healthy viable tissue. Although panretinal photocoagulation is the current medical practice for the treatment of diabetic retinopathy and is effective in inhibiting diabetic retinal neovascularization, this procedure destroys healthy peripheral retinal tissue. This destruction of healthy tissue decreases the retinal metabolic demand and thereby reduces retinal ischemia driven neovascularization. A recent new laser procedure is being tested for the inhibition of ocular neovascularization. Photodynamic therapy (PDT) is a procedure in which a photoactivatable dye is given systemically followed by laser activation of the dye in the eye at the site of new blood vessel formation (Asrani & Zeimer, Br J Ophthalmol, 79(8):776-770, August, 1995; Asrani et al, Invest Ophthalmol. Vis Sci, 38(13):2702-2710, December, 1997; Husain et al, Ophthalmology, 104(8):242-250, August, 1997; Lin et al, Curr Eye Res, 13(7):513-522, July, 1994.) The photoactivated drug generates free oxygen radicals which seal the newly formed blood vessels. This procedure has been used in patients with the exudative form of macular degeneration and many patients show regression of their subretinal neovascular membranes. Unfortunately, it appears that the PDT induced inhibition of neovascularization is transient lasting only 6-12 weeks (Gragoudas et al, Investigative Ophthalmology & Visual Science, 38(4):S17, March 15, 1997; Sickenberg et al, Investigative Ophthalmology & Visual Science, 38(4):S92, March 15, 1997; Thomas et al, Investigative Ophthalmology & Visual Science, 39(4):S242, March 15, 1998.)

The subject matter of the present invention involves combining the PDT induced regression of ocular neovascular tissue with agents, such as angiostatic steroids, which inhibit new blood vessel formation.

5    **Summary of the Invention**

This invention is directed to methods for treating ocular neovascular diseases by combining the use of PDT with particular angiostatic steroids.

**Brief Description of the Drawing**

10       **Figure 1** - Compares the ability of angiostatic steroids to inhibit neovascularization in the rabbit cornea.

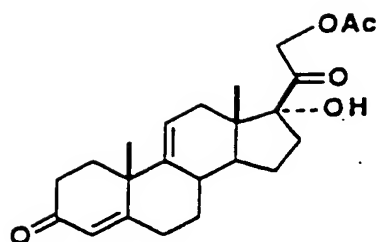
**Detailed Description Of The Preferred Embodiments**

15       The development of blood vessels for the purpose of sustaining vital tissue is known as angiogenesis or neovascularization. Agents which inhibit neovascularization are known by a variety of terms such as angiostatic, angiolytic, or angiotropic agents. For purposes of this specification, the term "angiostatic agent" means compounds which can be used to inhibit neovascularization.

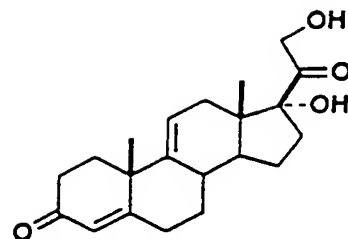
20       Ocular neovascularization has not been successfully treated in the past. Neovascularization of tissues in the front of the eye (i.e. the cornea, iris, and the trabecular meshwork) and other conditions, including conditions in the back of the eye, for example, retinal, subretinal, macular, and optical nerve head neovascularization, can be prevented and treated by administration of the steroids of this invention. The angiostatic agents are useful in  
25       preventing and treating ocular neovascularization, including providing for the regression of neovascularization.

      The angiostatic agents of this invention are steroids available from Steraloids, Inc., Wilton, N.H. and have the following structures and names:

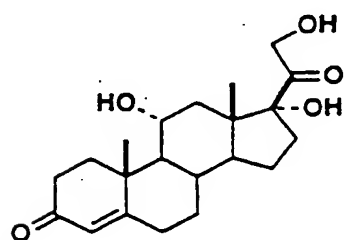
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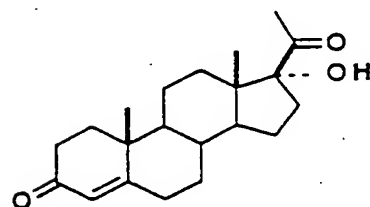
4,9(11)-Pregnadien-17a,21-diol-  
3,20-dione-21-acetate



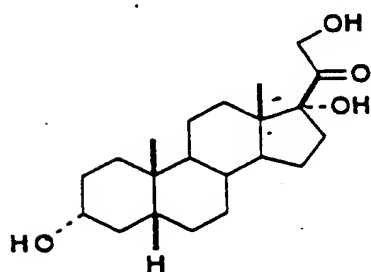
4,9(11)-Pregnadien-17a,21-  
diol-3,20-dione



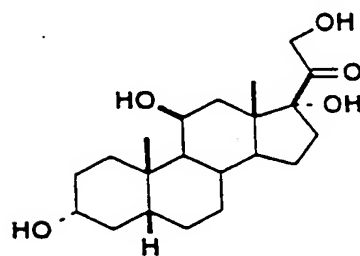
11-Epicortisol



17alpha-Hydroxyprogesterone



Tetrahydrocortexolone (THS)



Tetrahydrocortisol (THF)

The above structures include all pharmaceutically acceptable salts of the angiostatic steroids.

5

The preferred angiostatic steroids are 4,9(11)-pregnadien-17 $\alpha$ ,21-diol-3,20-dione and 4,9(11)-pregnadien-17 $\alpha$ ,21-diol-3,20-dione-21-acetate (anecortave acetate).

The angiostatic steroids in combination with PDT are useful in preventing and treating  
10 any ocular neovascularization, including, but not limited to: retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, age related macular degeneration (ARMD) due to subretinal neovascularization); rubeosis iritis; inflammatory diseases; chronic uveitis; neoplasms (retinoblastoma, pseudoglioma); Fuchs' heterochromic iridocyclitis; neovascular glaucoma; corneal neovascularization (inflammatory, transplantation,  
15 developmental hypoplasia of the iris); neovascularization resulting following a combined vitrectomy and lensectomy; vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia); neovascularization of the optic nerve; and neovascularization due to penetration of the eye or contusive ocular injury. In particular, this therapy is useful in the treatment of exudative ARMD and diabetic retinopathy.

20

The initiation of new blood vessel formation may arise quite differently in various tissues or as a result of different diseases. Many substances have been found to induce neovascularization, see, Folkman, et al., *Angiogenic Factors*, Science, Volume 235, pp. 442-447 (1987). However, it is believed, that once initiated, the process of neovascularization is similar  
25 in all tissues and regardless of the associated disease, Furcht, *Critical Factors Controlling Angiogenesis: Cell Products, Cell Matrix, and Growth Factors*, Laboratory Investigation, Volume 55, No. 5, pp. 505-509 (1986).

There are a variety of theories regarding the mechanism of action of angiostatic steroids.  
30 For example, angiostatic steroid induced inhibition of neovascularization may occur due to, dissolution of the capillary basement membrane, Ingber, et al., *Supra*; inhibition of vascular

endothelial cell proliferation, Cariou, et al., *Inhibition of Human Endothelial Cell Proliferation by Heparin and Steroids*, Cell Biology International Reports, Vol. 12, No. 12, pp. 1037-1047 (December, 1988); effect on vascular endothelial cell laminin expression, Tokida, et al., *Production of Two Variant Laminin Forms by Endothelial Cells and Shift of Their Relative Levels by Angiostatic Steroids*, The Journal of Biological Chemistry, Vol. 264, No. 30, pp. 18123-18129 (October 25, 1990); inhibition of vascular cell collagen synthesis, Maragoudakis, et al., *Antiangiogenic Action of Heparin Plus Cortisone is Associated with Decreased Collagenous Protein Synthesis in the Chick Chorioallantoic Membrane System*, The Journal of Pharmacology and Experimental Therapeutics, Vol. 251, No. 2, pp. 679-682 (1989); and inhibition of vascular endothelial cell plasminogen activator activity, Ashino-Fuse, et al., *Medroxyprogesterone Acetate, An Anti-Cancer and Anti-Angiogenic Steroid, Inhibits the Plasminogen Activator in Bovine Endothelial Cells*, Int. J. Cancer, 44, pp. 859-864 (1989).

There are many theories associated with the cause of neovascularization, and there may be different inducers depending on the disease or surgery involved, BenEzra, *Neovasculogenetic Ability of Prostaglandins, Growth Factors, and Synthetic Chemoattractants*, American Journal of Ophthalmology, Volume 86, No. 4, pp. 455-461, (October, 1978). Regardless of the cause or the associated disease or surgery, it is believed that angiostatic agents work by inhibiting one or more steps in the process of neovascularization. Therefore, the angiostatic steroids of this invention are useful in the treatment and prevention of neovascularization associated with a variety of diseases and surgical complications.

The angiostatic steroids of the present invention may be incorporated in various formulations for delivery to the eye. For example, topical formulations can be used and can include ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, buffers, sodium chloride, and water to form aqueous sterile ophthalmic solutions and suspensions. In order to prepare sterile ophthalmic ointment formulations, an angiostatic steroid is combined with a preservative in an appropriate vehicle, such as mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations comprising the angiostatic steroids of the present invention can be prepared by suspending an angiostatic steroid in a hydrophilic base prepared from a combination of, for example, Carbopol (a carboxy vinyl polymer available



the BF Goodrich Company) according to published formulations for analogous ophthalmic preparations. Preservatives and antimicrobial agents may also be incorporated in such gel formulations. Ocular injection (intravitreal, subtenons, subconjunctival, periocular, retrobulbar) as well as intraocular slow release devices and implants may be used, particularly for delivery to the back of the eye. Systemic formulations, for example, orally ingested tablets and formulations for intraocular injection are also contemplated.

The specific type of formulation selected will depend on various factors, such as the angiostatic steroid or its salt being used, the dosage frequency, and the location of the neovascularization being treated. Topical ophthalmic aqueous solutions, suspensions, ointments, and gels are the preferred dosage forms for the treatment of neovascularization in the front of the eye (the cornea, iris, trabecular meshwork); or neovascularization of the back of the eye if the angiostatic agent can be formulated such that it can be delivered topically and the agent is able to penetrate the tissues in the front of the eye. The angiostatic steroid will normally be contained in these and other formulations in an amount from about 0.01 to about 15.0 weight/percent. Preferable concentrations range from about 0.1 to about 7.5 weight/percent. Thus, for topical administration, these formulations are delivered to the surface of the eye one to six times a day, depending on the routine discretion of the skilled clinician. Systemic administration, for example, in the form of tablets is useful for the treatment of neovascularization particularly of the back of the eye, for example, the retina. Tablets containing 10-100 mg of angiostatic agent can be taken 2-3 times per day depending on the discretion of the skilled clinician.

The compounds, no matter how delivered, can be administered prior to, during, and/or after PDT. It is preferred to administer the compounds both before and after surgery to slow or prevent the reoccurrence of neovascularization.

The following examples illustrate formulations of the present invention, but are in no way limiting.

**Example 1****Topical Ocular Formulation**

	<b><u>Ingredient</u></b>	<b><u>Amount (wt.%)</u></b>
5	Anecortave Acetate	1.0
	Tyloxapol	0.01 to 0.05
10	HPMC	0.5
	Benzalkonium Chloride	0.01
	Sodium Chloride	0.8
15	Edetate Disodium	0.01
	NaOH/HCl	q.s. pH 7.4
20	Purified Water	q.s. 100 mL

The formulation is prepared by first placing a portion of the purified water into a beaker and heating to 90°C. The hydroxypropylmethylcellulose (HPMC) is then added to the heated water and mixed by means of vigorous vortex stirring until all of the HPMC is dispersed. The resulting mixture is then allowed to cool while undergoing mixing in order to hydrate the HPMC. The resulting solution is then sterilized by means of autoclaving in a vessel having a liquid inlet and a hydrophobic, sterile air vent filter.

The sodium chloride and the edetate disodium are then added to a second portion of the purified water and dissolved. The benzalkonium chloride is then added to the solution, and the pH of the solution is adjusted to 7.4 with 0.1M NaOH/HCl. The solution is then sterilized by means of filtration.

The 4,9(11)-Pregnadien-17 $\alpha$ ,21-diol-3,20-dione-21-acetate is sterilized by either dry heat or ethylene oxide. If ethylene oxide sterilization is selected, aeration for at least 72 hours at 50°C is necessary. The sterilized 4,9(11)-Pregnadien-17 $\alpha$ ,21-diol-3,20-dione-21-acetate is

weighed aseptically and placed into a pressurized ballmill container. The tyloxapol, in sterilized aqueous solution form, is then added to the ballmill container. Sterilized glass balls are then added to the container and the contents of the container are milled aseptically at 225 rpm for 16 hours, or until all particles are in the range of approximately 5 microns.

5

Under aseptic conditions, the micronized drug suspension formed by means of the preceding step is then poured into the HPMC solution with mixing. The ballmill container and balls contained therein are then rinsed with a portion of the solution containing the sodium chloride, the edetate disodium and benzalkonium chloride. The rinse is then added aseptically to the HPMC solution. The final volume of the solution is then adjusted with purified water and, if necessary, the pH of the solution is adjusted to pH 7.4 with NaOH/HCl. The formulation will be given topically, in a therapeutically effective amount. In this instance, the phrase "therapeutically effective amount" means an amount which is sufficient to substantially prevent or reverse any ocular neovascularization. The dosage regimen used will depend on the nature of the neovascularization, as well as various other factors such as the patient's age, sex, weight, and medical history.

15

### Example 2

#### Topical Ocular Formulation

20

	<u>Ingredient</u>	<u>Amount (wt.%)</u>
	Anecortave Acetate	1.0
25	Mannitol	2.40
	Sodium Chloride	0.40
	Carbopol 974P	0.50
30	Polysorbate 80	0.05
	Edetate Disodium	0.01
35	Benzalkonium Chloride	0.01 + 5% XS
	Sodium Hydroxide	adjust pH to 7.2
	Purified Water	qs to 100%

Example 3

## Tablet:

5 5-100 mg anecortave acetate with inactive ingredients such as starch, lactose and magnesium stearate can be formulated according to procedures known to those skilled in the art of tablet formulation.

Example 4

## Formulation for Sterile Intraocular Injection

each mL contains:

10	4,9(11)-Pregnadien-17 $\alpha$ ,21-diol-3,20-dione	10-100 mg
15	Sodium Chloride	7.14 mg
	Potassium Chloride	0.38 mg
	Calcium chloride dihydrate	0.154 mg
	Magnesium chloride hexahydrate	0.2 mg
	Dried sodium phosphate	0.42 mg
20	Sodium bicarbonate	2.1 mg
	Dextrose	0.92 mg
	Hydrochloric acid or sodium hydroxide	
	to adjust pH to approximately 7.2	
	Water for injection	

**Example 5****Sterile Injection Formulation**

	<b><u>List of Components</u></b>	<b><u>mg/ml</u></b>
5	Anecortave Acetate	0.1-150 (0.0 for vehicle)
	Monobasic Sodium Phosphate, Monohydrate	0.1-5
	Diabasic Sodium Phosphate, Anhydrous	0.1-5
10	Tyloxapol	0.0-10
	Sodium Chloride	0.1-10
15	Hydrochloric Acid and/or Sodium Hydroxide	Adjust pH 7.0 - 7.8
	Water for Injection	q.s.

20

**Example 6****Sterile Injection Formulation**

	<b><u>List of Compounds</u></b>	<b><u>mg/ml</u></b>
25	Anecortave Acetate	60
	Monobasic Sodium Phosphate, Monohydrate	0.45
	Dibasic Sodium Phosphate, Anhydrous	2.0
30	Tyloxapol	4.0
	Sodium Chloride	7.0
35	Hydrochloric Acid and/or Sodium Hydroxide	Adjust pH 7.4 ± 0.2
	Water for Injection	q.s

40

### Example 7

Inhibition of angiogenesis in the rabbit corneal neovascularization model:

5

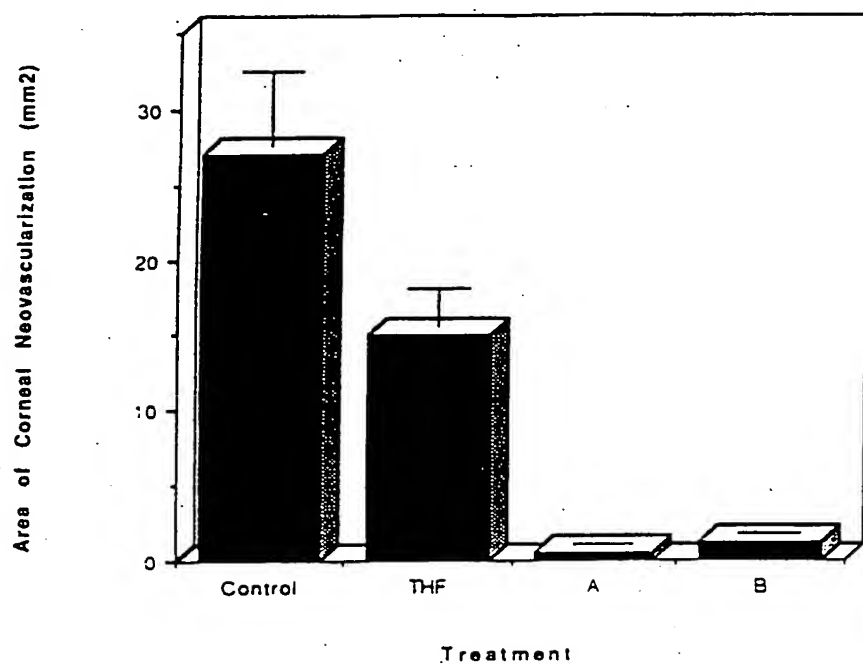
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The corneal pocket system of BenEzra (Am. J. Ophthalmol 86:455-461, 1978) was used to induce corneal neovascularization in the rabbit. A small Elvax pellet containing 0.5µg of lipopolysaccharide (LPS) was inserted into the middle of the corneal stroma and positioned 2.5 mm from the limbus. An additional Elvax pellet with or without 50µg of angiostatic steroid was placed next to the LPS implant. The eyes were examined daily and the area of neovascularization calculated. Results after 8 days of LPS implantation are shown in Figure 1. THF - tetrahydrocortisol; A = 4,9(11)-Pregnadien-17 $\alpha$ ,21-diol-3,20-dione-21-acetate; B = 4,9(11)-Pregnadien-17 $\alpha$ ,21-diol-3,20-dione. As can be seen, A & B totally inhibited corneal neovascularization, whereas THF partially inhibited the neovascular response.

**I Claim:**

1. A method for preventing and treating ocular neovascularization, which comprises the use of PDT in combination with a compound selected from the group consisting of: 4,9(11)-Pregnadien-17 $\alpha$ ,21-diol-3,20-dione-21-acetate, 4,9(11)-Pregnadien-17 $\alpha$ ,21-diol-3,20-dione, 11-Epicortisol, 17 $\alpha$ -Hydroxyprogesterone, Tetrahydrocortexolone (THS), and Tetrahydrocortisol (THF).
2. The method of Claim 1 wherein the angiostatic steroid is 4,9(11)-Pregnadien-17 $\alpha$ ,21-diol-3,20-dione-21-acetate.
3. The method of Claim 1 wherein the angiostatic steroid is 4,9(11)-Pregnadien-17 $\alpha$ ,21-diol-3,20-dione.
4. The method of Claim 1 wherein the angiostatic steroid is administered at a concentration of about 0.01 to 15.0 weight percent.
5. The method of Claim 4 wherein the angiostatic steroid is administered at a concentration of about 0.1 - 7.5 weight percent.

**FIGURE 1****EFFECT OF ANGIOSTATIC STEROIDS ON CORNEAL NEOVASCULARIZATION**



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/12711

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K41/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 371 078 A (CLARK ABBOT F ET AL) 6 December 1994 see column 2, line 31-50 see column 10, line 11-43; examples 1,2	1-5
Y	WO 91 19731 A (UPJOHN CO) 26 December 1991 see claims 15,19,20; example 1	1-5
Y	DATABASE DISSERTATION ABSTRACTS University Microfilms International Order NO: AAD97-35970, 1996 DEFALLER JOSEPH MICHAEL: "Mechanism of action and clinical efficacy of AL-3789, an angiostatic steroid" XP002082569 see abstract	1-5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"S" document member of the same patent family

Date of the actual completion of the international search

29 October 1998

Date of mailing of the international search report

12/11/1998

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/12711

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>VERINDER S. NIRANKARI: "Laser Photocoagulation for Corneal Stromal Vascularization" TRANS. AM. OPHTALMOL. SOC., vol. 90, 1992, pages 565-669, XP002082566 see page 599-600 see page 604-605 see page 655, last paragraph - page 656, last paragraph</p>	1-5
Y	<p>WO 95 24930 A (MASSACHUSETTS EYE &amp; EAR INFIRM) 21 September 1995 see page 3, line 30 - page 4, line 17; claims 1,2; examples 1-4</p>	1-5
Y	<p>MILLER J W ET AL: "PHOTODYNAMIC THERAPY OF EXPERIMENTAL CHOROIDAL NEOVASCULARIZATION USING LIPOPROTEIN-DELIVERED BENZOPORPHYRIN" ARCHIVES OF OPHTHALMOLOGY, vol. 113, no. 6, June 1995, pages 810-818, XP000672344 see the whole document</p>	1-5
Y	<p>COWLED P.A. ET AL.: "Potentiation of Photodynamic Therapy with Haematoporphyrin Derivatives by Glucocorticoids" CANCER LETTERS, vol. 29, 1985, pages 107-114, XP002081606 see the whole document</p>	1-5
Y	<p>ANDERSON C. ET AL.: "Phtalocyanine Photodynamic Therapy: Disparate effects of Pharmacologic Inhibitors on Cutaneous Photosensitivity and on Tumor Regression" PHOTOCHEMISTRY AND PHOTOBIOLOGY, vol. 65, no. 5, May 1997, pages 895-901, XP002082567 see page 895, column 1 see page 896, last paragraph See discussion page 900 * see page 898, column 1</p>	1-5
P,Y	<p>ABBOT F. CLARK: "AL-3789: a novel ophtalmic angiostatic steroid" EXPERT. OPIN. INVEST. DRUGS., vol. 6, no. 12, December 1997, pages 1867-1877, XP002082568 see the whole document</p>	1-5

# INTERNATIONAL SEARCH REPORT

International application No.

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## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 1-5  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/12711

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